Epilepsy & Behavior 62 (2016) 85–89

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial

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ARTICLE INFO

Article history:
Received 30 April 2016
Revised 7 June 2016
Accepted 8 June 2016
Available online 21 July 2016

Keywords:
Epilepsy
Sudden unexpected death in epilepsy
T-wave alternans
Biomarker
Risk reduction

ABSTRACT

Objective: Reports of cardiac arrhythmias and cardiac pathology at postmortem examination of patients with epilepsy suggest a possible cardiac component of risk for sudden unexpected death in epilepsy (SUDEP). T-wave alternans (TWA) is an established marker of cardiac electrical instability and risk for sudden death in patients with cardiovascular disease. We determined the TWA level before vagus nerve stimulation (VNS) system implantation and subsequently the effect of VNS on TWA in patients with drug-resistant epilepsy.
Methods: Patients (n = 28) from the Seizure Detection and Automatic Magnet Mode Performance Study (E-36), a clinical trial of the AspireSR® VNS Therapy System® (NCT01325623), were monitored with ambulatory electrocardiograms (ECGs) ~2 weeks before *de novo* VNS system implantation and following 2- to 4-week VNS titration during a protocol-specified 3- to 5-day epilepsy monitoring unit stay with concurrent EEG/ECG recordings. The TWA level was assessed interictally by the Modified Moving Average (MMA) method.
Results: At preimplantation baseline, TWA was elevated above the 47-μV abnormality cutpoint in 23 (82%) patients with drug-resistant epilepsy. In 16 (70%) patients, TWA level was reduced during VNS treatment to <47 μV, thereby converting positive TWA test results to negative. Peak TWA level in all 28 patients improved (group mean, 43%, from 72 ± 4.3 to 41 ± 2.3 μV; $p < 0.0001$). Vagus nerve stimulation was not associated with reduced heart rate (77 ± 1.4 to 75 ± 1.4 beats/min; $p = 0.18$). Heart rate variability was unchanged.
Significance: These findings suggest significant interictal cardiac electrical instability in this population of patients with drug-resistant epilepsy and suggest that VNS may be a novel approach to reducing risk.

1. Introduction

Approximately 40% of patients with epilepsy have seizures that do not respond adequately to antiepileptic drug therapy [1], a condition that is an established risk factor for sudden unexpected death in epilepsy (SUDEP). Biomarkers other than recurrent seizures for determining and monitoring SUDEP risk are currently unavailable.

Microvolt T-wave alternans (TWA), a subtle, beat-to-beat fluctuation in the morphology and amplitude of the ST segment or T-wave in the electrocardiogram, is a biomarker for cardiac electrical instability that correlates with risk for sudden cardiac death (SCD) in patients with cardiovascular disease [2]. During the postictal period in a group of patients with focal epilepsy, Strzelczyk et al. [3] reported markedly elevated levels of TWA. In a pilot study, we found interictal TWA levels in excess of the 47-μV cutpoint of abnormality in 100% (9 of 9) of patients with drug-resistant epilepsy and, furthermore, that interictal TWA was significantly reduced in association with vagus nerve stimulation (VNS) [4], suggesting an effect through alterations in autonomic tone and/or direct effects on myocardial substrate. Peak TWA level was converted from positive to negative in 67% (4 of 6) of patients.

The objective of the present study was to confirm and further extend these published pilot results by examining the impact of a combination of routine intermittent (open-loop) VNS and automatic (closed-loop) VNS on TWA in a larger subset of patients with drug-resistant epilepsy

Abbreviations: ARREST, Amsterdam Resuscitation Studies; AspireSR, Seizure Detection and Automatic Magnet Mode Performance Study; EMU, epilepsy monitoring unit; HF HRV, high-frequency heart rate variability; HRV, heart rate variability; LF HRV, low-frequency heart rate variability; MMA, Modified Moving Average; SCD, sudden cardiac death; SUDEP, sudden unexpected death in epilepsy; TWA, T-wave alternans; VNS, vagus nerve stimulation.

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http://dx.doi.org/10.1016/j.yebeh.2016.06.016

enrolled at multiple sites in the Seizure Detection and Automatic Magnet Mode Performance Study (E-36). Effects of VNS on autonomic nervous system tone and heart rate were also assessed. Our hypotheses were that interictal TWA would be elevated preimplantation and reduced in association with VNS.

2. Methods

2.1. Patient selection

The Seizure Detection and Automatic Magnet Mode Performance Study (E-36) (NCT01325623) was a prospective, multicenter study of VNS with the AspireSR Model 106 VNS Therapy® System implantable pulse generator (Fig. 1) in patients with drug-resistant epilepsy and a history of ictal tachycardia (defined either as 55% or a 35-beats/min increase in heart rate to ≥100 beats/min near seizure onset) (N = 30) [5]. The study conformed to the Declaration of Helsinki and was approved by the Competent Authorities and Ethics Committees at the participating centers. All patients signed informed consent. Patients were implanted between April 2011 and June 2013 at 13 European sites. To be eligible, patients also had to be at least 18 years old, be clinically diagnosed with drug-resistant epilepsy dominated by focal seizures, have an average of 3 or more seizures per month in the 3 months prior to the screening visit, and otherwise be in general good health and ambulatory. Patients were excluded if they had contraindications for the existing labeling for VNS, significant psychiatric or addictive disorders, a history of status epilepticus within 3 months of enrollment, were prescribed drugs specifically for a cardiac or autonomic nervous system disorder that potentially affected heart rate, had known clinically meaningful cardiovascular arrhythmias (including bradycardia), or had clinically meaningful cardiovascular arrhythmias determined by a 24-hour Holter recording obtained at the baseline visit.

Implantation techniques, postoperative care, and ramp-up and maintenance stimulation protocols were according to standard-of-care practices. All patients were naïve with respect to implantation of the leads and the generator. Vagus nerve stimulation settings were as follows: intensity, 0.75 mA and pulse width, 250 μs (medians). Pulse frequency was 20 Hz, and duty cycle was 30 s on followed by 5 min off. The individual settings were established by clinical personnel without knowledge of TWA status. Medications were not altered during the study period.

2.2. Ambulatory ECG recording and analysis

The patients' 24-hour electrocardiograms (ECGs) were recorded on a single day at baseline 2 weeks prior to VNS implantation and, following 2- to 4-week VNS titration, during the final seizure-free 24 h of the protocol-specified 3- to 5-day hospitalization in an epilepsy monitoring unit (EMU). The ECGs of 2 patients were not interpretable, leaving 28 subjects for our report. The baseline ECG and the ECG recorded on the final seizure-free day of the EMU stay were analyzed.

The TWA level was quantified with the Modified Moving Average (MMA) method [6] in standard precordial leads V_1, V_5, and aVF by an investigator (BDN) blinded to treatment status using the MARS Ambulatory ECG Analysis System (GE Healthcare, Milwaukee, WI). The conventional AECG configurations of V_1, V_5, and aVF provide satisfactory reliability from one recording to another from the same individual. The maximum interictal TWA level throughout the recording is reported as the TWA value for that patient. As established in patients with heart disease [2], a TWA cutpoint of ≥47 μV was defined in this study as an abnormal TWA test and ≥60 μV as markedly abnormal while TWA <20 μV was taken to indicate relative cardiac electrical stability.

Heart rate and HRV data were automatically generated by the GE Healthcare MARS version 8.0 software for the interictal period during the first hour of the recording. Heart rate variability (HRV) was analyzed in the frequency domain using the Fast Fourier spectral transform. Accordingly, the beat stream of the RR interval series was transformed to compute high-frequency (HF) power within the frequency band 0.150 to 0.400 Hz and low-frequency (LF) power within the frequency band 0.040 to 0.150 Hz, reported in milliseconds squared. The LF/HF ratio was calculated as LF frequency divided by HF frequency and is unitless. High-frequency heart rate variability (HF HRV) is a general indicator of parasympathetic tone, while LF HRV and the LF/HF HRV ratio are indicators of autonomic tone and balance [7]. Normative values of HF and LF HRV are 975 ± 203 and 1170 ± 416 ms^2, respectively, while an LF/HF HRV ratio of 1.5 to 2.0 is considered normal [7].

2.3. Statistical methods

The TWA level, HRV, and heart rate associated with VNS in AspireSR were analyzed by Student's t-test using SAS statistical package (SAS Institute, Cary, NC, USA). Fisher's exact test (two-tailed) was used to assess the significance of the change in percentage of patients with abnormal (≤47 μV) and severely abnormal (≤60 μV) TWA comparing levels before implant with levels at 2- to 4-weeks postimplant. Data are reported as means ± S.E.M., with $p < 0.05$ considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics are as described in detail by Boon et al. [5]. Briefly, all of the patients were Caucasian, and 19 (68%) were female. Mean age at onset of epilepsy was 16 years (range: 2–43) and at study enrollment was 40 years (range: 19–66).

3.2. Baseline interictal TWA levels

At baseline (preimplantation), interictal TWA was elevated to the ≥60-μV cutpoint of severe abnormality in 19 (68%) of the 28 patients and ≥47-μV abnormality cutpoint in 23 patients (82%). None of the patients had TWA <20 μV.

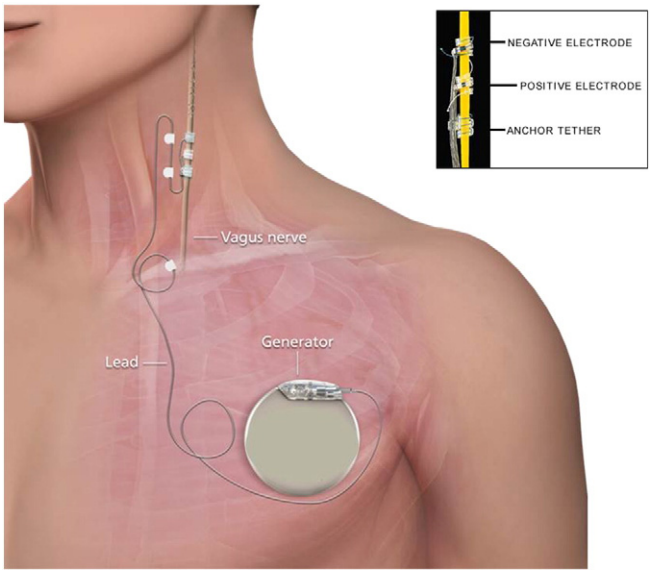

Fig. 1. Placement of vagus nerve stimulation device. As illustrated in the insert (upper right box), the distal end of the lead is wrapped around the nerve. The most proximal electrode is helical and helps to anchor the lead to the vagus nerve. The ECG sensing vector is from the generator can to the negative electrode.

3.3. Effect of VNS on interictal TWA levels and heart rate

Vagus nerve stimulation was associated with a decrease in TWA from baseline to the EMU stay in all 28 patients by a mean of 43% (from 72 ± 4.3 to 41 ± 2.3 μV; $p < 0.0001$) (Fig. 2) (Table 1). In 16 (70%) of these 23 patients, TWA was reduced from above to below 47 μV, thereby converting positive TWA test results to negative (Fig. 3). In 5 patients (18%), TWA remained below 47 μV, and in 7 patients (28%), TWA remained above 47 μV. In no patient did TWA convert from negative to positive. There were no statistically significant correlations between VNS stimulation current intensity, duty cycle, or the product of stimulation current intensity times duty cycle with the reduction in TWA during the EMU stay, which is expected given that all patients were at similar levels of output current and duty cycle. Vagus nerve stimulation was not associated with reduced heart rates in the group as a whole (77 ± 1.4 to 75 ± 1.4 beats/min; $p = 0.18$) (Table 1).

3.4. No alteration in heart rate variability following VNS implantation

Frequency-domain HRV measures did not change from baseline throughout the 3- to 5-day EMU stay (Table 1). However, LF HRV was in the normal range during the EMU stay, while HF HRV remained abnormally low and LF/HF ratio remained elevated when compared with standards in the literature [7].

4. Discussion

4.1. Main findings

We [4] and others [3] have previously demonstrated that TWA, an established electrocardiographic indicator of risk for life-threatening cardiac arrhythmias in patients with heart disease as well as advanced renal disease, is elevated between and during seizures, respectively, in patients with drug-resistant epilepsy. We have also reported that TWA is reduced in direct proportion to current strength of VNS in patients with either epilepsy [4] or heart failure [8].

The present study confirms and extends the results of our previous pilot study [4]. Prior to VNS therapy, the average TWA level was 72 ± 3.9 μV. This level of TWA is comparable with that associated with high risk for sudden death in patients with myocardial infarction, heart failure, advanced renal disease, or channelopathies including long QT [9] and Brugada syndromes [10]; although, notably, none of the patients in this study had a history of any of these conditions.

In this study of patients with drug-resistant epilepsy enrolled in the AspireSR E-36 trial, automatic VNS was associated with a highly significant reduction in interictal TWA level in all 28 patients ($p < 0.0001$). Nearly three-quarters (70%) of the patients with abnormal TWA levels experienced conversion from positive to negative TWA test results. These findings are also consistent with previous results in another patient cohort [4]. It is highly germane that levels of TWA were reduced after 3 weeks of VNS therapy by >20 μV to 41 ± 2.3 μV ($p < 0.001$), since with each 20-μV increase in TWA, cardiac mortality and SCD risk in populations without epilepsy increase by 55% and 58%, respectively [11]. The degree of TWA reduction documented in this study, therefore, carries the implication of reduced risk for cardiac mortality in the studied patients.

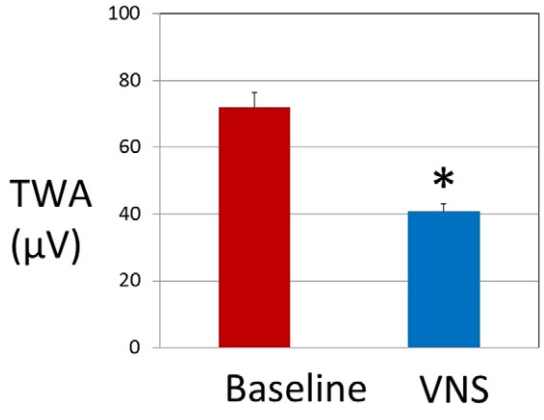

Fig. 2. Summary data in 28 patients with interpretable EKGs in the E-36 study showing a significant reduction in TWA in response to magnet-mode vagus nerve stimulation (VNS).

Table 1
Efficacy measures for 28 patients enrolled in the AspireSR TWA substudy.

Variable	Baseline	EMU	Significance
Heart rate (beats/min)	77 ± 1.4	75 ± 1.4	0.18
T-wave alternans (μV)	72 ± 4.3	41 ± 2.3	<0.0001
TWA ≥47 μV (N, %)	23 (82%)	7 (25%)	<0.0001
TWA ≥60 μV (N, %)	19 (68%)	2 (7%)	<0.0001
Heart rate variability LF (ms^2)	500 ± 57.0	900 ± 265.4	0.17
Heart rate variability HF (ms^2)	191 ± 30.5	193 ± 29.8	0.94
Heart rate variability LF/HF ratio	3 ± 0.4	4 ± 0.4	0.12

4.2. Implications of elevated TWA in patients with epilepsy

Patients with epilepsy may exhibit cardiac effects of seizures that can contribute to premature morbidity and SCD and/or SUDEP [12,13]. Enhanced arrhythmia susceptibility [13] and concomitant myocardial ischemia [14] have been implicated as critical factors. Neural triggering of ictal cardiac arrhythmias has been suggested as a factor in SUDEP [15]. Increased ictal cardiac sympathetic nerve activity is indicated not only by ictal surges in heart rates to >150 beats/min but also by persistence into the postictal period [16] and by heart rate variability analysis [17].

The hyperadrenergic state associated with seizures may constitute a major component of arrhythmia risk by directly triggering rhythm disturbances as well as through promoting cardiac pathology including myocardial fibrosis and degeneration in up to 33% of cases [18] and by accelerating atherosclerosis [19], conditions that set the stage for ventricular arrhythmia, perhaps especially so in association with ictal hypoxemia [20]. Autopsy investigations have revealed that the hearts of victims of SUDEP were characteristically dilated and heavier than expected [21]. The changes have been attributed to repeated episodes of hypoxemia [22] and/or increased catecholamine levels [18]. Increased

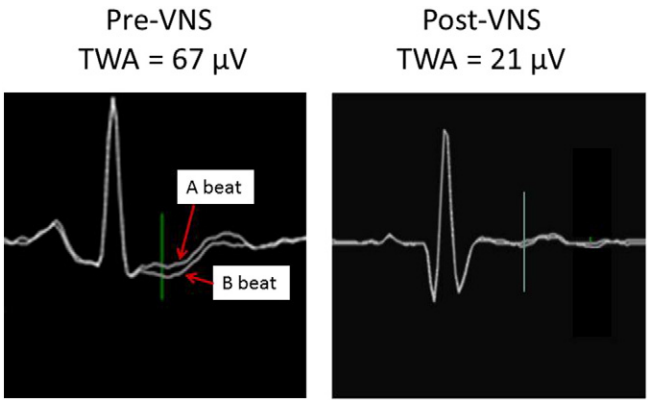

Fig. 3. Assessment of T-wave alternans (TWA) using the Modified Moving Average method in a representative patient with drug-resistant epilepsy performed before and after 4 weeks following vagus nerve stimulator (VNS) implantation, when the device was operating at planned levels. Templates of QRS-aligned superimposed beats reveal a separation in the morphology of the A and B beats, reflecting the ABABAB pattern between the J point and T-wave, which is the alternation hallmark of TWA and its electrophysiologic basis for estimating risk for arrhythmic death. In this patient, tracings from before (left) and after VNS implantation (right) indicate a reduction in TWA from 67 μV, which is above the ≥47 μV cutpoint for abnormality, to 21 μV.

serum levels of cardiac troponin I, indicative of myocardial injury, have been documented following uncomplicated epileptic seizures [23]. The incidence of myocardial infarction is also greater in patients with epilepsy than in the general population [24].

Case reports of ictal ventricular fibrillation in SUDEP and near-SUDEP cases have been published [25]. However, Stecker and Chugh concluded from their analysis of the Oregon Sudden Unexpected Death Study that SUDEP did not typically occur in association with seizures [26]. Nevertheless, a diagnosis of epilepsy increases risk for SCD by 3-fold (adjusted OR: 2.9 [95% CI: 1.1–8.0]; $p = 0.034$) over the general population, as reported in the community-based Amsterdam Resuscitation Studies (ARREST) [27]. These investigators concluded that cardiovascular disease rather than epilepsy characteristics is the main determinant of VT/VF in people with epilepsy and that SCD and SUDEP are partially overlapping disease entities [28]. Thus, these observations suggest that SUDEP associated with cardiac arrhythmia could potentially, in some instances, be triggered by factors other than seizures in vulnerable patients.

4.3. Potential mechanisms for cardiac protection

Explaining the precise mechanisms whereby VNS could reduce TWA in patients with drug-resistant epilepsy is particularly challenging in light of the multifactorial effects of chronic VNS. Two general pathways are likely to be involved. Specifically, it is likely that influences on the central nervous system can contribute to reduction in risk for arrhythmia, potentially by suppression of seizure activity. However, whether reduction in TWA by VNS correlates with decreased incidence of seizures remains to be established, and there are mixed reports of the capacity of VNS to reduce SUDEP of any cause [29,30]. Second, VNS is known to exert pleiotropic protective effects via peripheral influences. These include reduction in inflammation, cytokine expression, apoptosis, heart rate, and sympathetic nerve effects [31–35]. Because the latter two influences have been shown to affect TWA magnitude directly [2], they are strong putative mechanisms that require further investigation.

Excessive sympathetic nerve activity independent of heart rate can increase TWA, and its antagonism can reduce TWA. Vagus nerve stimulation is antisympathetic through classic mechanisms involving accentuated antagonism [36] and inhibition of stellate ganglion activity [32]. It is relevant that left-sided VNS is effective in reducing TWA, as Shen et al. [37] have shown that stimulation of the left vagus nerve results in ipsilateral inhibition of the left stellate ganglion. This structure exerts a major influence on susceptibility to VF, as evidenced by the effectiveness of left stellectomy in reducing SCD [38]. The recent findings that TWA is reduced in association with VNS therapy and that HRT slope, a measure of baroreceptor sensitivity [39], is improved in the ANTHEM-HF study of patients with heart failure [8] also implicate effects on autonomic reflexes in VNS-mediated reduction in TWA. While heart rate has been implicated as a factor in TWA level, it is not likely to have played a major role in the present study as heart rate was not reduced in the group as a whole.

In the future, it will be important to determine the persistence of the reduction in TWA in patients treated with VNS and beyond the setting of the telemetry unit. However, it is encouraging that, after one year of VNS in ANTHEM-HF, TWA remained reduced [8].

4.4. Conclusions and implications

The findings support our hypotheses and confirm previous pilot data, showing that interictal TWA is elevated preimplantation and reduced in association with VNS in patients with drug-resistant epilepsy. The magnitude of the effect on TWA is highly significant, with all patients showing a reduction and with a 70% conversion rate from positive to negative test results. We further extended our previous pilot data by showing in this study that significant reductions in TWA can occur after only three weeks of VNS. Taken together, these observations implicate a cardiac basis for SUDEP that can be assessed with TWA, which should be further studied as both a biomarker and a therapeutic target and the potential for reduced risk for cardiac-mediated SUDEP with VNS.

Funding

This study was funded by a grant VERR004 from LivaNova, Inc. to Beth Israel Deaconess Medical Center (BIDMC), RL Verrier, P.I.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

Drs. Verrier and Nearing receive royalty from Georgetown University and BIDMC for the Modified Moving Average method for TWA analysis, which is licensed by GE Healthcare. Dr. Olin is employed by LivaNova, PLC. Drs. Boon and Schachter declare no conflicts of interest.

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